REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	13-October-2000	Final Report

4. TITLE AND SUBTITLE

Effects of Electromagnetic Fields on the Blood Brain Barrier

5. FUNDING NUMBERS

F61775-99-WE010

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8. PERFORMING ORGANIZATION REPORT NUMBER

N/A

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

EOARD
PSC 802 BOX 14
FPO 09499-0200

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

SPC 99-4010

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

A

13. ABSTRACT (Maximum 200 words)

This report results from a contract tasking Lund University Hospital to investigate the effects of electromagnetic fields (EMF) in the 915-2450 MHz range on the permeability of the blood brain barrier (BBB) in rats. Male and female Fischer rats were exposed to continuous wave or pulse-modulated EMF, with different pulse powers and times up to 960 minutes. Albumin and fibrinogen were demonstrated immunohistochemically in perfused brains and classified as normal vs. pathological leakage. Leakage in exposed rats was significantly increased vs. controls. Researchers found no pronounced difference between various modulation frequencies, though continuous radiation seemed more effective in opening the BBB. There also appeared to be a biphasic closing of the opened BBB, including a fast component with a half-time of about 20 min and a more prolonged slow component. Studies related to global system for mobile communication (GSM) microwave exposures showed increased BBB permeability with GSM-900, 217-Hz modulation as well as with GSM-1800. Although results indicated that microwave exposure produced an effect on the BBB in rats, researchers noted that their method for detecting albumin leakage across the BBB was extremely sensitive and felt that small amounts of leakage detected may be harmless.

14. SUBJECT TERMS

EOARD, Physiology, Radio Frequency Safety and Health

15. NUMBER OF PAGES

38

16. PRICE CODE

N/A

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19, SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. 239-18
298-102

DTIC QUALITY INSPECTED 4

20010108 023

EFFECTS OF ELECTROMAGNETIC FIELDS ON THE BLOOD BRAIN BARRIER

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AQ F01-04-0691

Executive Summary:

Biological effects of RADIO FREQUENCY electromagnetic fields (EMF) on the blood-brain barrier (BBB) have been studied in Fischer 344 rats of both sexes. The rats were not anaesthetised during the exposure. All animals were sacrificed by perfusion-fixation of the brains under chloralhydrate anaesthesia after the exposure. The brains were perfused with saline for 3-4 minutes, and thereafter perfusion fixed with 4% formaldehyde for 5-6 minutes. Whole coronal sections of the brains were dehydrated and embedded in paraffin and sectioned at 5 µm. Albumin and fibrinogen were demonstrated immunohistochemically and classified as normal versus pathological leakage.

In the present investigation we exposed male and female Fischer 344 rats in a Transverse Electromagnetic Transmission line chamber to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated with different pulse power and at various time intervals. The CW-pulse power varied from 0.001W to 10 W and the exposure time from 2 min. to 960 min. In each experiment we exposed 4 rats with 4 controls randomly placed in excited and non-excited TEM-cells respectively.

We have in total investigated 630 exposed rats at various modulation frequencies and 372 controls. The frequency of pathological rats is significantly increased ($p<0.0001$) from 62/372 (ratio: 0.17±0.02) for control rats to 244/630(ratio: 0.39±0.03) in all exposed rats. Grouping the exposed animals according to the level of specific absorbed energy (J/kg) give significant difference in all levels above 1.5 J/kg.

The exposure was 915 MHz microwaves either pulse modulated (PW) at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width or continuous wave (CW). The frequency of pathological rats (< 0.2) among controls in the various groups is not significantly different. The frequency of pathological rats was 170/481(0.35±0.03) among rats exposed to pulse modulated (PW) and 74/149 (0.50±0.07) among rats exposed to continuous wave exposure (CW). These results are both highly significantly different to their corresponding controls ($p<0.0001$) and the frequency of pathological rats after exposure to pulsed radiation (PW) is significantly less ($p<0.002$) than after exposure to continuous radiation (CW).

We found no pronounced difference between the various modulation frequencies other than the effect of CW seems to be more effective in opening the BBB. This is surprising since the common opinion is that modulated microwaves would be more biologically effective.

There seems to be no difference in the degree of opening the BBB with the time of exposure that might indicate a switch mechanism that is turned on by the microwaves but turned off again by the brain

There seems to be a biphasic relaxation of closing the opened BBB with a fast component with a halftime of about 20 min. There is also a slow component which has a very long halftime of about 200 000 min which means that some parts of the BBB stay open for a long time.

The effects of global system for mobile communication (GSM) microwave exposure on the permeability of the blood-brain barrier are of special interest. Thus GSM pulse sequence of 217 Hz modulation with 0.52 ms pulse width was studied in 169 rats exposed to various SAR levels as well as 24 rats exposed to real GSM-900 modulated microwaves. The results related to exposure with GSM-900 and 217 Hz modulation frequencies were significant at both very low SAR levels ant at higher levels. There is a good agreement between our results and those presented by Fritze et al. (1997). Their results show an increase in serum albumin extravasations after microwave exposure (p=0.01, Fisher exact probability test) in all groups if cage controls and sham exposed rats are used as controls. Rats exposed to the highest SAR of 7.5 W/kg and the bulked 0.3+1.5 W/kg groups show significant leakage when only sham controls are used in t-test.

We have found that also exposure to GSM-1800 results in BBB openings at various SAR level. When all 61 exposed animals are t-tested against their 103 controls there is a significant difference (p=0.03).

Differences in BBB permeability in Fischer 344 rats exposed to microwaves of various frequency has been studied with both 915 MHz and 1800 MHz continuous wave. At both frequencies there was highly significant difference in the BBB permeability between exposed and controls

Several summaries of epidemiological studies concerning neurological diseases and EMF have been published (Bergqvist et al. 1998;Feychting et al. 1998;Johansen & Olsen 1998;Savitz, Chekoway, & Loomis 1998;Savitz, Loomis, & Tse 1998)

The results from these studies do not indicate any distinct correlation between EMF and the risk to develop Alzheimer's disease and Parkinson's disease. The biological hypothesis concerning EMF and these diseases are still missing.

The conclusive results from those studies indicate, however, a significant increased risk of ALS (amyotrophic lateral sclerosis) in groups in occupation related to high EMF exposure. The risk seems to increase with exposure that indicates a dose-response relation. A possible mechanism for increased risk of ALS is EMF induced production of antibodies that induce premature ageing of the large nerve cells that are affected in ALS. The disturbed function of the Ca-channels in these cells is probable involved in the ageing process.

These findings motivate further studies in order to determine the level of health risks involved from human exposure to microwaves.

The enhanced permeability of the blood brain barrier found in rats exposed to microwaves might also be involves in the mechanism of induction of neurological disease (Persson et al. 1999;Persson, Salford, & Brun 1997a;Salford & Persson 1998a;Salford, Persson, & Brun 1997a)

At present we have ongoing studies concerning late histopathological effects where rats are are examined at various time points after exposure.

We are also examining the effect of combined microwave and ELF exposure. All these experiments are under histopathological evaluation and it will take some more months until we have the results available.

INTRODUCTION

The mammalian brain is protected from exposure to potentially harmful compounds in the blood by the so-called "*Blood-brain barrier*" (BBB). The BBB is a hydrophobic barrier formed by vascular endothelial cells with very tight junctions between endothelial cells. This results in a highly restricted passage of blood components through the endothelial lining. Selective transport mechanisms mediated by receptors in the cell membrane guarantee the import of essential compounds such as glucose, and export of metabolites through the BBB (Oldendorf 1975;Rapoport 1976).

Astrocytes are covering the inner of the endothelial cells with their end feet and are implicated in the maintenance, functional regulation and repair of the blood-brain barrier. Thus BBB also serves as a regulatory system that stabilises and optimises the fluid environment of the brain's intracellular compartment (Oldendorf 1975;Rapoport 1976). The intact BBB protects the brain from damage, whereas a dys-functioning BBB, allows influx of normally excluded hydrophilic molecules into the brain tissue. This might lead to cerebral oedema, increased intrakranial pressure and in the worst case, irreversible brain damage.

The normal selective permeability of the blood-brain barrier (BBB) can be altered in several pathological conditions such as epileptic seizures or extreme hypertension (Mihaly & Bozoky 1984;Mihàly & Bozòky 1984;Sokrab et al. 1988a;Sokrab et al. 1988b). The blood brain barrier system has been used to investigate effects on CNS of various types of physiological activity and stress and has also found to be sensitive to electromagnetic energy. In **Table 1** is given a review of investigations reported that microwave exposure of rats increase BBB permeability to various compounds.

In **Table 2** is given a review of those studies that did not reveal any increased BBB permeability from microwave or RF exposure. In the most recent report Tsurita et al. 1999 exposed rats with 1.439 GHz microwaves from cellular phone at an average SAR of 0.25 W/kg for 2-4 weeks and found no evidence of albumin leakage with the same method we have used (Tsurita et al. 1999).

Since 1988 we have studied the permeability of BBB to endogenous albumin and fibrinogen during exposure to electromagnetic fields. We have exposed rats to various magnetic and magnetic fields as well as 915 MHz microwaves as continuous wave (CW) and pulse-modulated at the various repetition rates (50-200 pulses per s) (Persson & Salford 1996;Persson, Salford, & Brun 1996;Persson, Salford, & Brun 1997b;Persson, Salford, & Brun 1997c;Salford et al. 1992;Salford et al. 1993b;Salford et al. 1993a;Salford et al. 1994b;Salford et al. 1994a;Salford & Persson 1998b;Salford, Persson, & Brun 1997b).

MATERIAL AND METHODS

Exposure in a TEM-cell

A Transverse Electromagnetic transmission line cell (TEM-cell) used for the RF exposure of rats was designed by dimensional scaling from previously constructed cells at the

National Bureau of Standards (Crawford 1974). TEM-cells are known to generate uniform TEM-fields for standard measurements

The cell is enclosed in a wooden box that supports the outer conductor and central plate. The outer conductor is made of brass-net and is attached to the inner walls of the box. The centre plate, or septum, is constructed of aluminium and is held up by Teflon braces, which are screwed at the inner sidewalls.

To allow access to the inside of the cell both ends can be removed. The inside of the cell is ventilated through 18 holes (diam. 18 mm) in the sidewalls and top of the box and the brass-net of 50 mesh allow air to circulate. These holes are also used for examination of the interior during exposure. Probes for monitoring temperature inside the cell or test object are inserted through these holes.

The rats are placed in plastic trays to avoid contact with the central plate and outer conducter. The bottom of the tray is covered with absorbing paper to collect urine and faeces.

EMBEDThe rats were exposed to 915 MHz electromagnetic radiation continuos wave and pulse-modulated with different repetition rates. The modulated RF-radiation consists of square wave shaped pulses with durations of 0.57, 4 or 6 ms and intensities (in Watts) during the presence of the pulse. Transmitted and absorbed power was measured at continuos wave exposure with and without rats in the TEM cell. From these measurements the average SAR in the whole rat was calculated to be 1.2 ± 0.4 W/kg per watt of input power. This value was in good agreement with the theoretical estimate of 1.6 W/Kg per watt of input power that was used in the evaluation of the experiment (Crawford 1974;Martens et al. 1992;Van Hese et al. 1991).

Albumin and fibrinogen immunohistochemistry

Fischer 344 rats of both sexes, weighing 119-555 g (median: 202 g; 25% quartiles: 175 g; 75% quartiles 273 g) were used in these experiments (own breeding). The rats were not anaesthetised, during the exposure.

Both controls and exposed animals were sacrificed by perfusion-fixation of the brains under chloralhydrate anaesthesia between 20 minutes and 2 hours after the exposure. The brains were perfused with saline for 3-4 minutes, thereafter fixed in 4% formaldehyde for 5-6 minutes and immersion fixed in 4% formaldehyde for more than 24 hours. Whole coronal sections of the brains (3, 7 and 11 mm from the tip of the frontal pole) were dehydrated and embedded in paraffin and sectioned at 5 m. The chloralhydrate anaesthesia is necessary to avoid stress and blood pressure rise during perfusion-fixation procedure. Also for ethical reason no animals were sacrificed without chloral hydrate anaesthesia.

Albumin was demonstrated with the IgG fraction of rabbit anti rat albumin (Cappel Research Products, Organon Teknika, Västra Frölunda, Sweden) diluted 1:16,000. Fibrinogen was demonstrated with rabbit anti human fibrinogen (Dacopatts AB, Hägersten, Sweden), diluted 1:500. Incubation time for both was over night at 4°C.

Biotinylated swine anti rabbit IgG was used as a secondary antibody. Then avidin, peroxidase conjugated, was coupled to the biotin and visualised with DAB (diaminobenzidine), counterstained with Meyer-HTX (Dacopatt 1994). Standard control procedures were used for both albumin and fibrinogen.

The numbers of immunopositive extravasates were recorded under a microscope. None or occasional minor leakage was rated as normal, whereas one larger or several leakages were regarded as pathological. Immunopositive sites were, however, disregarded when localised in the hypothalamus, basally from the median eminence and laterally including the nucleus

lateralis hypothalami, in the immediate vicinity of the third ventricles. These structures are well known for their insufficient blood-brain barrier and within any part of of the choroid plexus of the ventricles consitently shows immunopositivities, mostly of a diffuse type, in the strain used in the present experiments.

Statistics

The degree of albumin leakage was ranked by the neuropathologist "AB" according to the following order:

0 AB = normal brain with no sign of immunopositive extravasates
0.5 AB = normal brain with occasional minor immunopositive extravasates
1.0 AB = pathological leakage with one distinct immunopositive extravasate in each of the three brain slices.
1.5 AB = pathological leakage with several distinct immunopositive extravasate in each of the three brain slices.
2 AB = pathological leakage with massive distinct immunopositive extravasate in each of the three brain slices.
3 AB = pathological leakage with overwhelming number of massive immunopositive extravasate in each of the three brain slices.

The frequency of occurrence of albumin extravasations in exposed and control animals were compared with chi-square- or Fisher's exact probability test.

RESULTS AND DISCUSSIONS

Continuous wave (CW) and pulse-modulated 915 MHz microwaves

In the present investigation we exposed male and female Fischer 344 rats in a TEM-chamber to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated with different pulse power and at various time intervals. The CW-pulse power varied from 0.001W to 10 W and the exposure time from 2 min to 960 min. In each experiment we exposed 4 rats with 4 controls randomly placed in excited and non-excited TEM-cells respectively.

The number of pathological rat brains among all control rats is 62 out of 372 (ratio: 0.17±0.02). These findings are occasional and rare and are probably due to normal minor disturbances. The frequency of pathological rats among controls in the various groups is not significantly different ($p<0.4$). **Figure 1** is shown a typical section of the brain from a normal unexposed Fischer rat immunoassayed for albumin. In **Figure 2** is shown the brain from a Fischer 344 rat exposed with GSM_900 in which there is pathological leakage around vessels as demonstrated by immunostaining against albumin.

We have in total investigated 635 rats exposed with 915 MHz microwaves at various modulation frequencies and 371 controls. The frequency of pathological rats is significantly

increased ($p<0.0001$) from 62/371 (ratio: 0.17±0.02) for control rats to 244/635 (ratio: 0.39±0.03) in all exposed rats. All results are displayed in **Table 3** grouped in ascending SAR level . The exposure was 915 MHz microwaves either pulse modulated (PW) at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width or continuous wave (CW). The frequency of pathological rats (< 0.2) among controls in the various groups is not significantly different ($p<0.4$). The frequency of pathological rats was 170/481 (0.35±0.03) among rats exposed to pulse modulated (PW) and 74/149 (0.50 ±0.07) among rats exposed to continuous wave exposure (CW). These results are both highly significantly different to their corresponding controls ($p<0.0001$) and the frequency of pathological rats after exposure to pulsed radiation (PW) is significantly less ($p<0.002$) than after exposure to continuous radiation (CW) . The number of pathological leakage in exposed animals is more severe and more frequent per animal compared to the controls.

The results of BBB-permeability of albumin in rats exposed to 915 MHz microwaves with different modulation frequencies for groups exposed to SAR values $4 \cdot 10^{-4}$ - $8 \cdot 10^{-3}$ W/kg are displayed in **Figures 4**

The frequency of pathological rats was 170/481(0.35±0.03) among rats exposed to pulse modulated (PW) and 74/149(0.50±0.07) among rats exposed to continuous wave exposure (CW). These results are both highly significantly different to their corresponding controls ($p<0.0001$) and the frequency of pathological rats after exposure to pulsed radiation (PW) is significantly less ($p<0.002$) than after exposure to continuous radiation (CW). This is a highly interesting observation as the current opinion is that pulse modulated electromagnetic fields are more potent in causing biological effects.

GSM-900 modulated microwaves in TEM-cells,

The results for exposure of Fischer 344 rats in TEM-cells with modulated 900 MHz microwaves from a real GSM-900 mobile telephone are given in **Table 4.** The output power was controlled from a computer to study the effect of various SAR values. So far only the highest SAR level of 200 mW/kg has reached enough number of animals to get a significant effect. At the lowest SAR value was 0.2 mW/kg at which level there seems to be no albumin leakage.

GSM-900 modulated microwaves in anechoic chamber,

The results from exposure of 16 Fischer 344 rats in an anechoic chamber with 900 MHz GSM modulated microwaves from a real GSM-900 mobile telephone compared to 13 controls was not significant different. The ratio of albumin leakage score for exposed (1,3) and controls (1,2) was 1.1.

GSM-1800 modulated and CW microwaves in anechoic chamber,

Microwaves from a real GSM-1800 mobile telephone was amplified and transferred to the dipole antenna in the anechoic chamber. The output power was varied to study the effect of various SAR values.

The In **Figure 3** is shown the brain of a Fischer G rat (#4219 Male) exposed for 2 h with 1800-GSM at SAR: 0,027 mW/kg. The result of albumin leakage is ranked as 3 AB. The

results for exposure of Fischer 344 rats in an anechoic chamber with 1800 MHz GSM modulated or continuous wave are summarized in **Table 5.**

DISCUSSIONS

Modulation frequency dependence

The average score values of albumin leakage in Fischer 344 rats (controls and exposed with 915 MHz microwaves at various modulation frequencies) are displayed in **Figure 4.** There is no pronounced difference between the various modulation frequencies other than the effect of CW seems to be more effective in opening the BBB. This is surprising since the common opinion is that modulated microwaves would be more biologically effective.

SAR dependence

The histogram in **Figure 5** shows the average rank values ("AB") for BBB albumin leakage in Fischer 344 rats exposed to 915 MHz microwaves at SAR values. The number of rats in each group is displayed next to the bars. The upper line represent the ratio of the average rank values between exposed and controls. The SAR dependence is very similar to that previously reported for the microwave alteration of the blood-brain barrier system of rats (Oscar & Hawkins 1977).

Exposure time dependence

Changes in BBB permeability in Fischer 344 rats exposed to continuous microwaves at various time intervals are presented in **Figure 6** as weighted rank difference between exposed and matched sham exposed animals. There seems to be no difference in the degree of opening the BBB with the time of exposure that might indicate a switch mechanism that is turned on by the microwaves but turned of again by the brain

Lag time dependence

Differences in BBB permeability in Fischer 344 rats exposed to microwaves at various lag time lags between end of exposure and perfusion fixation is shown in **Figure 7.** There seems to be a biphasic relaxation of closing the opened BBB with a fast component with a halftime of about 20 min. The slow component has a halftime of about 200 000 min which means that some fraction never close very slowly.

Sex dependence

The average of all AB-rank values in 249 female Fisher rats of our own breed was 0.29± 0.03 (SEM) and in 114 males was 0.36±0.05 (SEM). Those values were however not statistically different p=0.18.

The average of all AB-rank values in 62 female Fisher rats imported from Germany was 1.20± 0.13 (SEM) and in 41 males it was 1.35±0.19 (SEM). Those values were however not statistically different p=0.52

BBB effects of global system for mobile communication (GSM)

The effect of global system for mobile communication (GSM) microwave exposure on the permeability of the blood-brain barrier is of special interest (**Table 3**). Thus GSM pulse sequence of 217 Hz modulations with 0.52 ms pulse width was studied as well as real GSM exposure (**Table 4**).

Another study used a calibrated microwave exposure system in the 900 MHz band. Rats were restrained in a carousel of circularly arranged plastic tubes and sham-exposed or microwave irradiated for a duration of 4 h at specific brain absorption rates (SAR) ranging from 0.3 to 7.5 W/kg. The extravasations of proteins was assessed either at the end of exposure or 7 days later in three to five coronal brain slices by immunohistochemical staining of serum albumin. The results are displayed in **Table 6**. Their results show an increase in serum albumin extravasations after microwave exposure (p=0.01, Fisher exact probability test) in all groups if cage controls and sham exposed rats are used as controls. Rats exposed to the highest SAR of 7.5 W/kg and the bulked 0.3+1.5 W/kg groups show significant leakage when only sham controls are used in t-test.

The results related to exposure with GSM-900 and 217 Hz modulation frequencies at various SAR levels are displayed in **Figure 8**. As can seen from this figure there is a good agreement between the results of (Fritze, Sommer, Schmitz, Mies, Hossmann, Kiessling, & Wiessner 1997)and or own results. In most of the groups there is a significant difference between exposed and controls. In some groups the ratio between exposed and controls are >1 with no significance, that is probably due to too few exposed animals.

We have found that also exposure to GSM-1800 results in BBB openings at various SAR level. When all 61 exposed animals are t-tested against their 103 controls there is a significant difference (p=0.03).

Microwave frequency dependence

Differences in BBB permeability in Fischer 344 rats exposed to microwaves of various frequency has been studied with both 915 MHz and 1800 MHz continuous wave. At both frequencies there was highly significant difference in the BBB permeability between exposed and controls. In **Figure 9** is shown the summary of ratio between exposed and control rats at various SAR values with corresponding p values also displayed.

Addendum

S-100 protein levels in blood from Fischer rats Exposed to CW microwaves

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S-100 is a calcium binding protein predominantly localized in the glia cells of the brain. Recent studies have shown that even minor skull injuries give rise to a leakage of S-100 to the blood. The level of S-100 in serum is normally very low and an increase level is an indication of a leakage through the cell walls of the glia and also through the BBB.

We have started a study where blood samples from rats exposed to microwaves (CW as well as GSM) for varying periods of time. Preliminary findings from a small number of rats exposed to CW [(1)] do not indicate any increased level as compared to controls. This is to our knowledge the first study on S-100 in rats and major efforts are required to further develop this track of research.

1. Salford L.G. and Persson BRR (2000) S-100 protein levels in blood from Fischer rats Exposed to CW microwaves. 2nd International Conference on Biochemical Markers for Brain Damage Lund Sweden 14-16 Sept, 2000

POTENTIAL HEALTH EFFECTS

Neurological diseases

Several summaries of epidemiological studies concerning neurological diseases and EMF have been published (Bergqvist, Brante, Fransson, Hansson Mild, Hillert, Johansson, Rönnbäck, Sandström, & Stenberg 1998;Feychting, Pedersen, Svedberg, Floderus, & Gatz 1998;Johansen & Olsen 1998;Savitz, Chekoway, & Loomis 1998;Savitz, Loomis, & Tse 1998)

The results from these studies do not indicate any distinct correlation between EMF and the risk of to develop Alzheimer's disease or Parkinson's disease. There is, however, a slight indication of a connection between highly exposed individuals and increased risk concerning these diseases. The biological hypothesis concerning EMF and these diseases are still missing.

The conclusive results from those studies indicate, however, a significant increased risk of ALS (amyotrophic lateral sclerosis) in groups in occupation related to high EMF exposure. The risk seems to increase with exposure that indicates a dose-response relation. A possible mechanism for increased risk to develop ALS, is EMF induced production of antibodies that induce premature ageing of the large nerve cells that are affected in ALS. The disturbed function of the Ca-channels in these cells is probably involved in the ageing process.

These findings motivate further studies in order to determine the level of health risks involved from human exposure to microwaves.

The enhanced permeability of the blood brain barrier found in rats exposed to microwaves might also be involved in the mechanism of induction of neurological disease (Persson, Malmgren, Salford, & Brun 1999;Persson, Salford, & Brun 1997a;Salford & Persson 1998a;Salford, Persson, & Brun 1997a)

CONCLUSION

We have demonstrated that microwave exposure produces an unequivocal effect on the BBB in Fischer rats. The clinical importance of this finding, however, is disputable. Our method for detection of albumin is extremely sensitive and reveals even minute amounts of albumin leaking through the BBB, so small that they may be harmless to the brain. However, the potential health hazards of the opening the BBB during exposure to wireless communication demands further investigation.

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Figure Captions

Figure 1
Brain section of non-exposed control rat immunoassayed for albumin.

Figure 2.
Pathological leakage around vessels demonstrated by immunostaining against albumin.
Fischer 344 rat exposed with GSM_900

Figure 3.
Pathological leakage around vessels demonstrated by immunostaining against albumin.
Fischer 344 (#4219 Male) exposed 2 h with 1800-GSM at SAR: 0,027 mW/kg
The result is ranked 3 AB.

Figure 4
The histogram shows the average rank values ("AB") for BBB albumin leakage in Fischer 344 rats exposed to 915 MHz microwaves modulated at various numbers of pulses per s (Hz). The p values represent the significance in difference from the controls. The line represent the ratios of the average rank values between exposed and controls. The number of rats in each group is displayed in the lowest line.

Figure 5
The histogram show the average rank values ("AB") for BBB albumin leakage in Fischer 344 rats exposed to 915 MHz microwaves at SAR values. The number of rats in each group is displayed next to the bars. The upper line represent the ratio of the average rank values between exposed and controls.

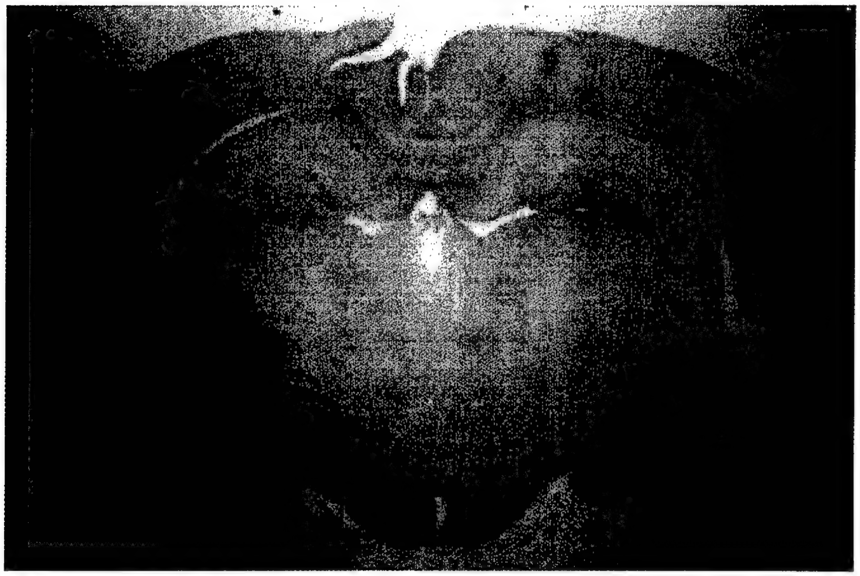


Figure 1

Brain section of non-exposed control rat immunostained for albumin.

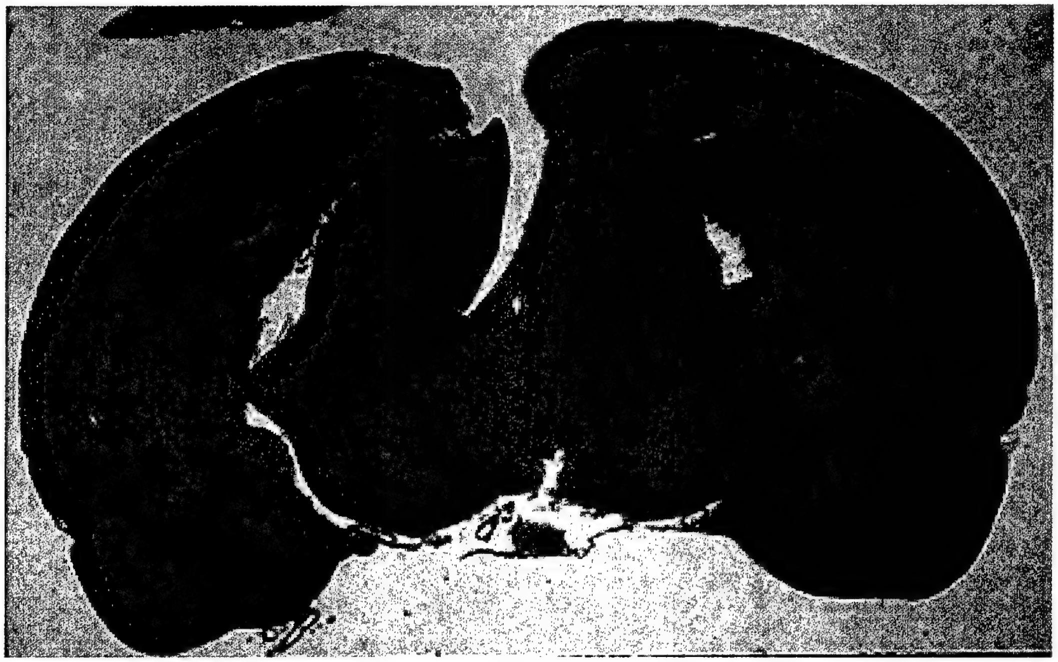
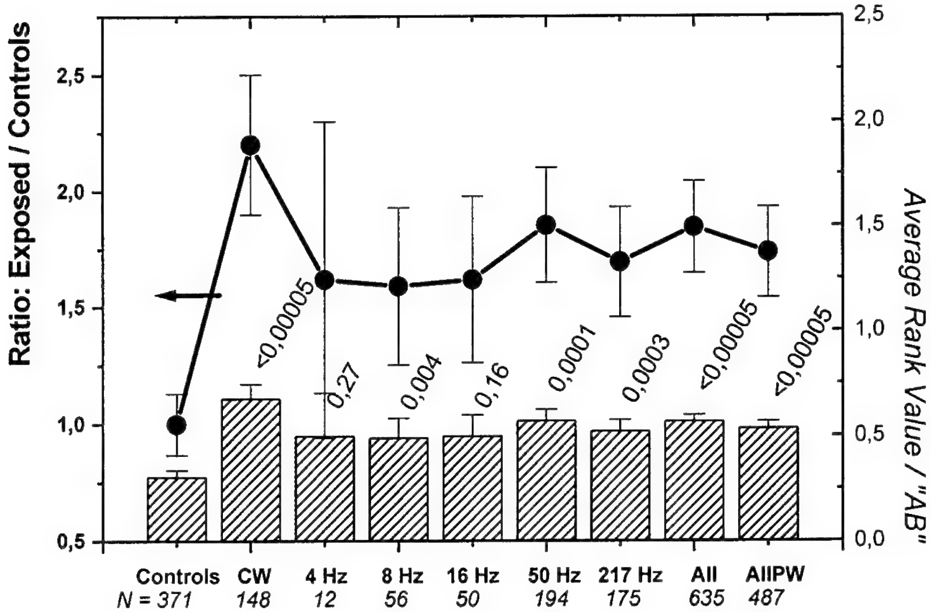


Figure 3

Pathological leakage around vessels demonstrated by immunostaining against albumin. Fischer 344 (#4219 Male) exposed 2 h with 1800-GSM at SAR: 0,027 mW/kg
The result is ranked 3 AB.



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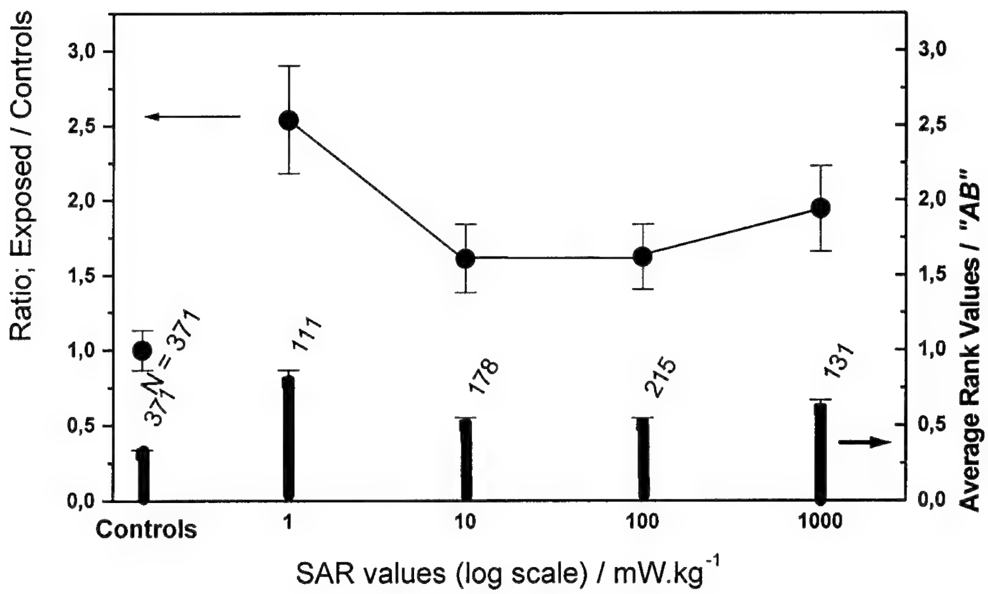
The histogram show the average rank values ("AB") for BBB albumin leakage in Fischer 344 rats exposed to 915 MHz microwaves modulated at various number of pulses per s (Hz). The p values represents the significance in difference from the controls. The line represent the ratios of the average rank values between exposed and controls. The number of rats in each group is displayed in the lowest line.



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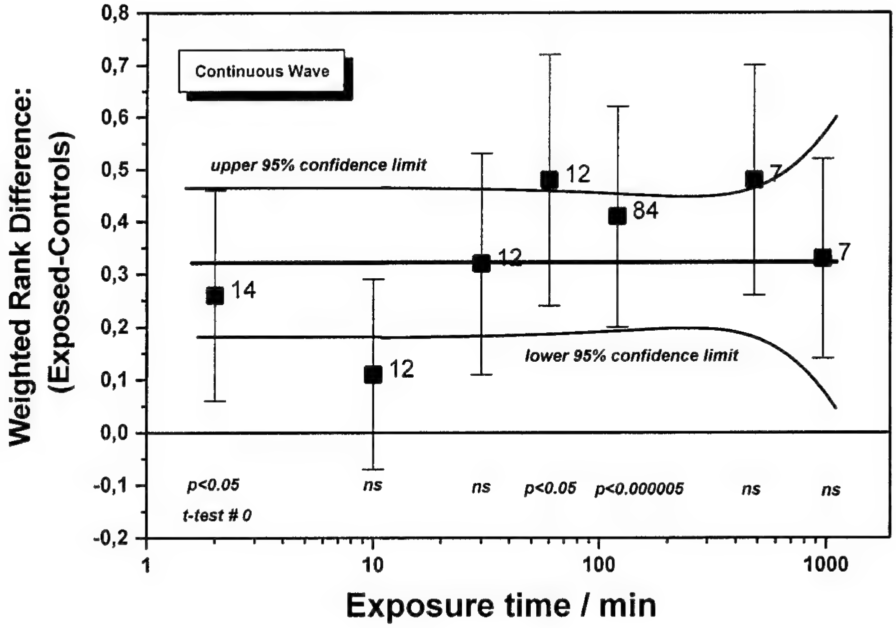

Figure 6

Changes in BBB permeability in Fischer 344 rats exposed to continuous wave microwaves at various time intervals presented as weighted rank difference between exposed and matched sham exposed animals.

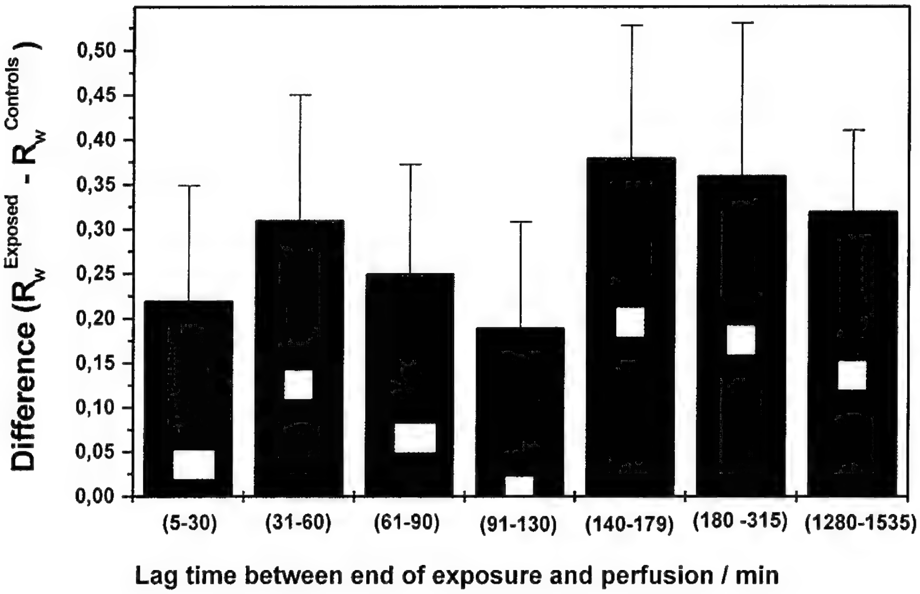

Figure 7

Differences in BBB permeability in Fischer 344 rats exposed to microwaves at various lag time lag between end of exposure and perfusion fixation. Number of rats in each group are displayed on the bars.

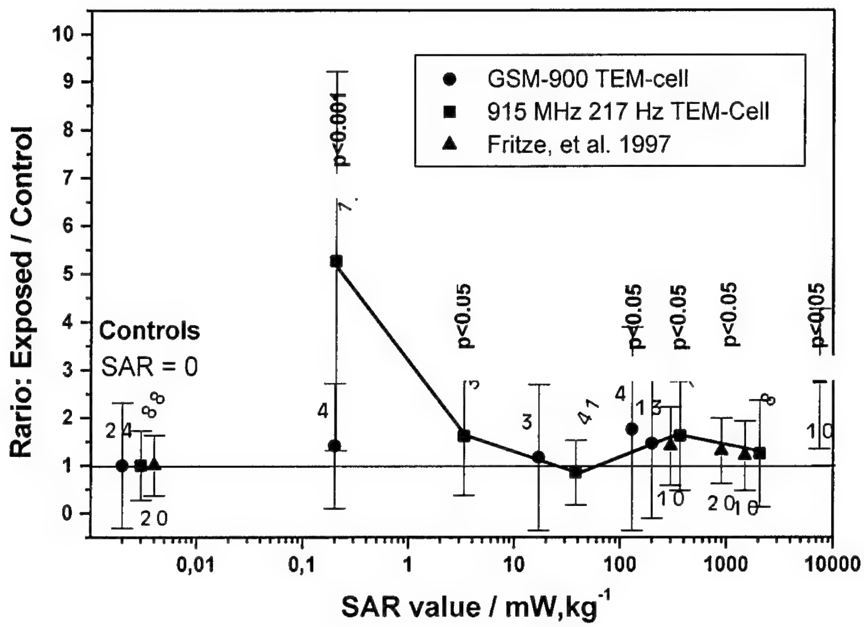

Figure 8

Summary of ratio between recorded immunostained albumin in Fischer 344 rats exposed to GSM-900 mdulated microwaves at various SAR values. The t-test p vales for ratios significant > 1 are also displayed.

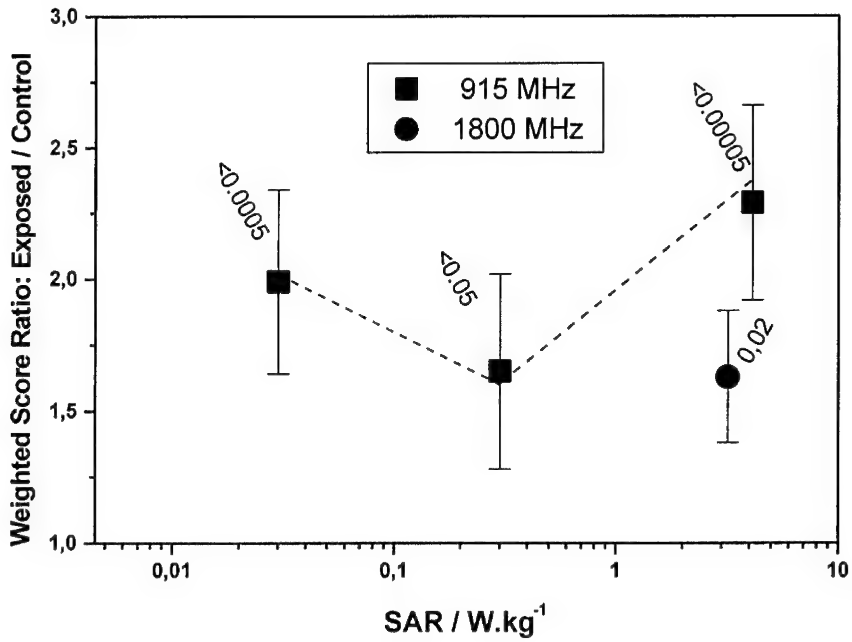

Figure 9

Summary of ratio between recorded immunostained albumin in Fischer 344 rats exposed Continuous Wave microwaves 0f 915 MHz and 1800 MHz at various SAR values. The p vales for ratios significant > 1 are also displayed.

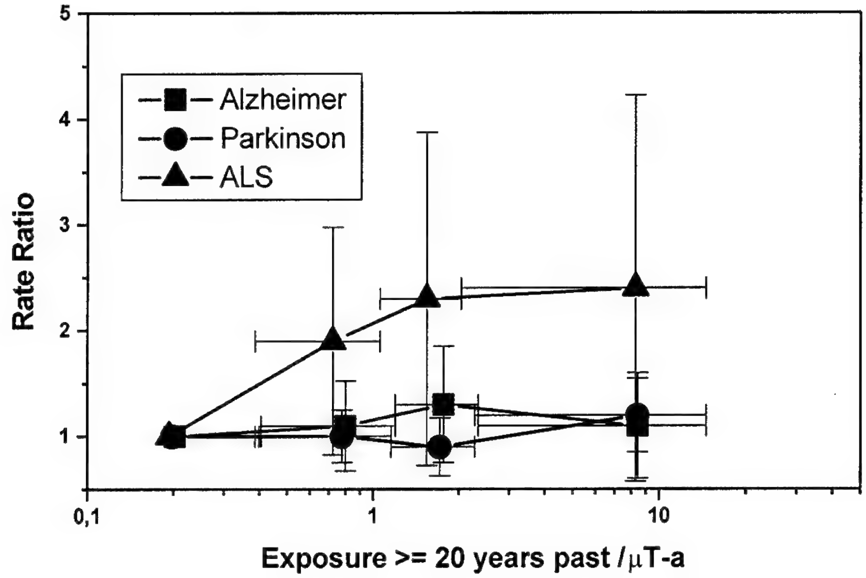

Figure 10

Summary of epidemiological studies concerning neurological diseases and occupational exposure to magnetic fields at more than 20 years. The results do not indicate any distinct correlation between EMF and the risk of Alzheimer's disease and Parkinson's disease. There is, however, a slight indication of a connection between highly exposed individuals and increased risk concerning these diseases. The biological hypothesis concerning EMF and these diseases are still missing.
{Savitz, Chekoway, et al. 1998 SAVITZ1998 /id}{Savitz, Loomis, et al. 1998 SAVITZ1998A /id}

SAR=	E-1							
Score	0	4	8	16	50	217	All Hz	All PW
0	14		8	8	43	25	98	84
0,5	4		2	5	14	12	37	33
1	13		2	5	25	21	66	53
1,5	0		0	0	8	2	10	10
2	1		0	0	1	2	4	3
3	0		0	0	0	0	0	0
Tot	32		12	18	91	62	215	183
SUM<1	18		10	13	57	37	135	117
Sum>=1	14		2	5	34	25	80	66
Ratio	0,44		0,17	0,28	0,37	0,40	0,37	0,36
SD	0,14		0,13	0,14	0,08	0,10	0,05	0,05
Chi2 p			0,80	0,37	<0,00005	<0,00005	<0,00005	<0,00005

SAR=	E+0							
Score	0	4	8	16	50	217	All Hz	All PW
0	20			4	16	12	5	32
0,5	13			0	9	4	2	13
1	29			2	5	4	4	11
1,5	5			0	0	0		0
2	5			0	1	0		1
3	1			0	1	0		1
Tot	73			6	32	20	13	58
SUM<1	33			4	25	16	7	45
Sum>=1	40			2	7	4	5	13
Ratio	0,55			0,33	0,22	0,20	0,4	0,22
SD	0,11			0,27	0,09	0,11	0,0	0,07
Chi2 p	<0,00005			0,60	0,61	0,94	<0,00005	0,38

SAR=	All							
Score	0	4	8	16	50	217	All Hz	All PW
0	46	4	24	20	76	75	245	199
0,5	28	4	13	14	39	46	144	116
1	58	4	16	14	61	38	191	133
1,5	9	0	2	0	13	5	29	20
2	6	0	1	2	4	10	23	17
3	1	0	0	0	1	1	3	2
Tot	148	12	56	50	194	175	**635**	487
SUM<1	74	8	37	34	115	121	389	315
Sum>=1	74	4	19	16	79	54	246	172
Ratio	0,50	0,33	0,34	0,32	0,41	0,31	0,39	0,35
SD	0,07	0,19	0,09	0,09	0,05	0,05	0,03	0,03
Chi2 p	<0,00005	0,27	0,004	0,16	0,0001	0,0003	<0,00005	<0,00005

371 Controls 635 exposed

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Table 1a.
Increased Blood-Brain Barrier permeability at microwave exposure of rats and mice at 2450 MHz and higher.

Reference	**Microwave Frequency MHz**	**Modulation Pulses per s "pps"**	**SAR W/kg**	**Tracer studied**	**Remark**
(Neilly & Lin 1986)	3150		3 W/cm^2	Ethanol & Evans Blue	Ethanol inhibits MW-induced BBB permeation of Evand Blue
(Albert 1979)	2800	0/CW	10 mW/cm^2	HRP[1)]	Reversed after 2 h delay
(Sutton, Nunnally, & Carroll 1973)	2450	0/CW	high	HRP[1)]	42°C in < 5min
(Sutton & Carrol 1979)	2450	0/CW	high	HRP[1)]	Temp. rise
(Albert 1977)	2450	0/CW	10 mW/cm^2	HRP[1)]	Permeability increase
(Albert & Kerns 1981)	2450	0/CW	2.5	HRP[1)]	Permeability increase
(Lin & Lin 1982)	2450	25-500	0.08-240	Evans Blue and Flourescine	Permeability increase at 240 W/kg not at lower SAR
(Goldman et al. 1984)	2450	500	240	Rubidium-86	Temp. increase
(Quock et al. 1986)	2450	0/CW	24	Methylatropin e	10 min exposure enhance BBB permeability
(Quock et al. 1987)	2450	0/CW	24	Domperidone	10 min exposure enhance BBB permeability

1) HRP = Horseradish peroxidase

(Continued)

Table 1b.
Increased Blood-Brain Barrier permeability at microwave exposure of rats and mice at 2450 MHz. (Continued)

Reference	Microwave Frequency MHz	Modulation Pulses per s "pps"	SAR W/kg	Tracer studied	Remark
(Neubauer et al. 1990)	2450	100	2	rhodamine-ferritin	A pino-cytotic-like mechanism is presumed responsible for the MW induced increase in BBB permeability
(Moriyama, Salcman, & Broadwell 1991)	2450	0/CW	?	HRP[1)]	Permeability increase accompanied by temp. increase
(Nakagawa et al. 1994)	2450	CW interstitial		MR T2 imaging	BBB disruption >43°C
(Frey, Feld, & Frey 1975)	1200	1000 &CW	0.2-2.4	Fluorescine	Permeability increase
(Oscar & Hawkins 1977)	1300	50-1000	0.3-2 mW/cm^2	mannitol, inulin, and dextran	Inversed U-shape dose/respon se
(Merritt, Chamness, & Allen 1978)	1200	1000	2-75 mW/cm^2	Fluorescin and ^{14}C-mannitol	Permeability increase only in hyper-thermic rats

[1)] HRP = Horseradish peroxidase

Table 1c.
Increased Blood-Brain Barrier permeability at microwave exposure of rats and mice at 915 MHz and lower.

Reference	Microwave Frequency MHz	Modulation Pulses per s "pps"	SAR W/kg	Tracer Studied	Remark
(Salford et al. 1992)	915	8-215		Evans Blue, albumin, fibrinogen	Permeability increase for albumin but not for fibrinogen
(Salford et al. 1993)	915	8-200	0.016-5	albumin and fibrinogen	Permeability increase for albumin but not for fibrinogen
(Persson, Salford, & Brun 1997)	915	0/CW 4-200	0.016-5	albumin and fibrinogen	Permeability increase for albumin but not for fibrinogen
(Fritze et al. 1997)	900	217	0.3-1.5	Albumin	Permeability increase at 7.5 W/kg, but not at lower SAR
(Persson et al. 1999)	900 and 1800	GSM	0.001-0.2	albumin and fibrinogen	Permeability increase for albumin but not for fibrinogen
(Prato et al. 1990)	65	0.4-28 T/s	Clinical MRI examinee.	^{153}Gd-DTPA	MRI increase BBB permeability

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Sutton, C. H., Nunnally, R. L., & Carroll, F. B. 1973, "Protection of the microwave-irradiated brain with body core hypothermia", *Cryobiology*, vol. 10, pp. 513-514.

Table 2a.
Non-increased Blood-brain barrier permeability at microwave exposure of rats and mice with frequency 2450 MHz.

Reference	**Microwave Frequency MHz**	**Modulation Pulses per s "pps"**	**SAR W/kg**	**Tracer Studied**	**Remark**
(Gruenau et al. 1982)	2800	500	240	^{14}C-sucrose	No increase
(Preston, Vavasour, & Assenheim 1979)	2450	CW and pulsed	0.1-30 mW/cm^2	^{14}C-sucrose	No permeability increase
(Ward et al. 1982)	2450	0/CW	2-6 W/kg	^{14}C-sucrose ^{3}H-inulin	No permeability increase
(Williams et al. 1984a)	2450	CW	13 (41°C)	Na-fluorescin,	Permeability increased but not BBB breakdown
(Williams, del Cerro, & Michaelson 1984)	2450	CW	13	HRP,	No extravasatio n of HRP
(Williams, Platner, & Michaelson 1984)	2450	CW	13	^{14}C-Sucrose	No increased leakage
(Williams et al. 1984b)	2450	CW	4	Na-fluorescin, HRP, ^{14}C-Sucrose	Suppression of BBB permeability at > 40°C
(Lin & Lin 1980)	2450	500 (10 μs pw)	0.04-240	Evans Blue "EB"	No uptake of EB <240 W7kg

Table 2b.
Non-increased Blood-brain barrier permeability at microwave exposure of rats and mice with frequency 1700 - 900 MHz.

Reference	Microwave Frequency MHz	Modulation Pulses per s "pps"	SAR W/kg	Tracer Studied	Remark
(Ward & Ali 1985)	1700	CW & 1000 (0.5μs pw)	0.1	^{14}C-Sucrose	No change in uptake
(Tsurita et al. 1999).	1439	CW	0.25	Evans Blue, albumin	No effect was found.
(Merritt, Chamness, & Allen 1978)	1200	1000 &CW	0.2-2.4	Fluorescine	repeat of Frey 1975
(Preston 1982;Preston & Prefontaine 1980;Preston, Vavasour, & Assenheim 1979)	1300	50-1000	0.3-2 mW/cm^2	mannitol, inulin, and dextran	no U-shape dose/respon se
(Fritze et al. 1997)	900	217 Hz (GSM)	0.3-7.5	Albumin	Modest, reversible extravasatio n

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Table 3
Summary of results from exposure with 915 MHz microwaves continuous wave and modulated at 4,8,16,50 and 217 Hz.

SAR=0	Controls							
Score	0	4	8	16	50	217	All	All PW
0	69	1	13	10	69	61	223	154
0,5	24	1	5	5	31	20	86	62
1	20	2	1	2	17	7	49	29
1,5	2	0	0	0	1	4	7	5
2	1	0	0	0	3	2	6	5
3	0	0	0	0	0	0	0	0
Tot	116	4	19	17	121	94	371	626
SUM<1	93	2	18	15	100	81	309	216
Sum>=1	23	2	1	2	21	13	62	39
Ratio	0,20	0,50	0,05	0,12	0,17	0,14	0,17	0,06
SD	0,05	0,43	0,05	0,09	0,04	0,04	0,02	0,01
Chi2 p	0,53	0,22	0,31	0,83	0,98	0,60	[redacted]	0,72

SAR=	E-3-E-4							
Score	0	4	8	16	50	217	All	All PW
0		4	2	0	5	12	23	23
0,5		4	5	2	5	21	37	37
1		4	8	3	9	7	31	31
1,5		0	2	0	2	3	7	7
2		0	1	1	2	8	12	12
3		0	0	0	0	1	1	1
Tot		12	18	6	23	52	111	111
SUM<1		8	7	2	10	33	60	60
Sum>=1		4	11	4	13	19	51	51
Ratio		0,33	0,61	0,67	0,57	0,37	0,46	0,46
SD		0,19	0,23	0,43	0,20	0,10	0,08	0,08
Chi2 p		0,27	<0,00005	0,01	<0,00005	0,001	<0,00005	<0,00005

SAR=	E-2							
Score	0	4	8	16	50	217	All Hz	All PW
0	12		14	8	12	26	72	60
0,5	11		6	7	11	9	44	33
1	16		6	4	22	6	54	38
1,5	4		0	0	3	0	7	3
2	0		0	1	0	0	1	1
3	0		0	0	0	0	0	0
Tot	43		26	20	48	41	178	135
SUM<1	23		20	15	23	35	116	93
Sum>=1	20		6	5	25	6	62	42
Ratio	0,47		0,23	0,25	0,52	0,15	0,35	0,31
SD	0,13		0,10	0,13	0,13	0,06	0,05	0,05
Chi2 p	<0,00005		0,57	0,51	<0,00005	0,91	<0,00005	<0,00005

SAR=	E-1							
Score	0	4	8	16	50	217	All Hz	All PW
0	14		8	8	43	25	98	84
0,5	4		2	5	14	12	37	33
1	13		2	5	25	21	66	53
1,5	0		0	0	8	2	10	10
2	1		0	0	1	2	4	3
3	0		0	0	0	0	0	0
Tot	32		12	18	91	62	215	183
SUM<1	18		10	13	57	37	135	117
Sum>=1	14		2	5	34	25	80	66
Ratio	0,44		0,17	0,28	0,37	0,40	0,37	0,36
SD	0,14		0,13	0,14	0,08	0,10	0,05	0,05
Chi2 p			0,80	0,37	<0,00005	<0,00005	<0,00005	<0,00005

SAR=	E+0							
Score	0	4	8	16	50	217	All Hz	All PW
0	20			4	16	12	5	32
0,5	13			0	9	4	2	13
1	29			2	5	4	4	11
1,5	5			0	0	0		0
2	5			0	1	0		1
3	1			0	1	0		1
Tot	73			6	32	20	13	58
SUM<1	33			4	25	16	7	45
Sum>=1	40			2	7	4	5	13
Ratio	0,55			0,33	0,22	0,20	0,4	0,22
SD	0,11			0,27	0,09	0,11	0,0	0,07
Chi2 p	<0,00005			0,60	0,61	0,94	<0,00005	0,38

SAR=	All							
Score	0	4	8	16	50	217	All Hz	All PW
0	46	4	24	20	76	75	245	199
0,5	28	4	13	14	39	46	144	116
1	58	4	16	14	61	38	191	133
1,5	9	0	2	0	13	5	29	20
2	6	0	1	2	4	10	23	17
3	1	0	0	0	1	1	3	2
Tot	148	12	56	50	194	175	**635**	487
SUM<1	74	8	37	34	115	121	389	315
Sum>=1	74	4	19	16	79	54	246	172
Ratio	0,50	0,33	0,34	0,32	0,41	0,31	0,39	0,35
SD	0,07	0,19	0,09	0,09	0,05	0,05	0,03	0,03
Chi2 p	<0,00005	0,27	0,004	0,16	0,0001	0,0003	<0,00005	<0,00005

371 Controls 635 exposed

Table 4
Summary of results from exposure with real GSM-900 modulated microwaves in TEM-cells

GSM-900 TEM cell	SAR mW/kg	N	Average	SD	E/C(SD)	SD	T-test
All Exposed	<200	24	1.04	0.59	1.47	1.60	0.07
All Controls	0	24	0.71	0.66			
Exposed 33dB	200	13	1.04	0.56	2,25	2.97	0.01
Controls 33	0	13	0.46	0.56			

Table 5.
Summary of results from exposure with real GSM-1800 modulated or CW microwaves in anechoic-cells,

Type of exposure	avearge	Sd	N	SE	Ratio E/C	t-test
GSM-1800	1,59	1,09	61	0,14	1,29	0,03
CW	2,00	0,90	12	0,26	1,63	0,02
Controls	1,23	1,08	103	0,11	1,00	

Table 6.

Effect of global system for mobile communication (GSM) microwave exposure on blood-brain barrier permeability in rat (Fritze et al. 1997)

	No. rats	No. positive albumin dots	SAR W/kg	Frequency positive albumin dots %	SD	t-test	Fisher-test	t-test	Fisher-test
Cage Control	20	1	0	5	5	versus	versus		
Sham Control	20	4	0	20	10	sham Control	sham Control	versus	versus
All controls	40	5	0	12.5	6			all Ctrls	all Ctrls
0.3 W/kg	10	7	0.3	70	26	0.10	0.08	0.06	0.01
1.5 W/kg	10	6	1.5	60	24	0.12	0.08	0.06	0.01
7.5 W/kg	10	14	7.5	140	37	0.03	0.08	0.03	0.01
0.3+1.5=0.9W/kg	20	13	0.9	65	18	0.02			

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